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Iodine supplementation in pregnancy and its effect on child cognition

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ABSTRACT

Maternal hypothyroidism and hypoxynaemia due to iodine deficiency have been shown to affect development of the newborn negatively. Maternal iodine supplementation may therefore improve cognitive performance of the offspring, even in areas of mild-to-moderate iodine deficiency (ID). Several iodine supplementation studies have been performed in mildly ID pregnant women in Europe. These studies have shown that iodine supplementation increases maternal urinary iodine (UI) excretion and reduces thyroid volume, as well as prevents increases in infant thyroid volume and thyroglobulin. However, randomized controlled studies with long-term outcomes are lacking. Therefore, two trials were started in 2008 in areas of low iodine status: one in Bangalore, India (n = 325), and another in Bangkok, Thailand (n = 514). Pregnant women were recruited <14 weeks gestational age and randomized to either receive a daily dose of 200 μg I (as KI) or an identical placebo throughout pregnancy. Both trials are ongoing, and women are followed up during pregnancy and at delivery. UI, thyroid hormones, and thyroid size are measured. Birth outcomes are recorded, such as gestational age at delivery, height, weight, and APGAR scores, and cord blood and heel stick blood (<72 h) is collected from the child. Child development is assessed at 6 weeks of age using the Neonatal Behavioral Assessment Scale (NBAS), and at 12 and 24 months of age using the Bayley Scales of Infant Development. The outcomes of these trials will contribute importantly to the evidence base for iodine supplementation of pregnant women living in areas of mild iodine deficiency.

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Iodine deficiency and its consequences for brain development

Iodine has since long been recognized as an important element for fetal growth and development [1]. Severe iodine deficiency during pregnancy is the cause of congenital hypothyroidism resulting in cretinism, an irreversible form of retarded growth and mental retardation. Cretinism used to be common in mountainous areas, such as the Alps, the Andes and the Himalaya where glaciers and erosion have depleted soils from iodine [2]. Cretinism, however, is confined only to a small group of individuals in a deficient population. A much larger proportion of a population living in an iodine deficient area is exposed to milder consequences, generally referred to as the iodine deficiency disorders (IDD) [3]. This comprises hypothyroidism and goiter, but also impaired cognition. It has been estimated that iodine deficiency ranks third on the list of causes that puts back children in their developmental potential [4]. Iodization of salt has been proven a highly successful means to incorporate iodine in the daily food supply of millions of people throughout the world [5]. According to WHO, there are currently no countries left where severe iodine deficiency is endemic, and to date, there are 32 countries remaining in the world where mild to moderate iodine deficiency is still a public health problem [6]. Iodine deficiency is not only a health threat in developing countries, but also in developed countries, especially in Europe. Recent reports suggest that iodine deficiency has recurred in countries where it had been under control previously, such as in the United States, Australia, New Zealand, and the United Kingdom [7,8].

Early studies have shown that maternal iodine supplementation indeed has a positive impact on the developmental quotient of children living in areas where severe iodine deficiency is common. A study done in Zaire showed that 6-year old children from supplemented mothers had a 10-point higher developmental score than their peers from non-supplemented mothers [9]. Similarly, a study in China showed a 15-point difference between 2-year old children from supplemented mothers as compared to children from non-supplemented mothers [10]. A frequently cited meta-analysis

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by Bleichrodt and Born states that moderate to severe iodine deficiency leads to a reduction of 12–13.5 IQ points in children [11]. A major limitation is that primarily cross-sectional studies were included in this meta-analysis, which therefore may have suffered from confounding. Moreover, many of the studies included were not peer reviewed, and no rigorous exclusion criteria were used. Many more studies with similar outcomes have been performed since, also in areas with less severe iodine deficiency [12–20]. Yet, confounding of the study results has mostly not been ruled out. It is also not always clear from these studies whether the reduction in IQ should be attributed to iodine deficiency in utero, or to iodine deficiency in later life. Intervention studies in school children do suggest, on the whole, that cognitive impairment related to mild-to-moderate iodine deficiency is, at least partly, reversible [21–28].

Should pregnant women in areas with mild deficiency be advised to take iodine supplements?

Since brain development starts very early in fetal life, it may well be that iodine has its most significant effect if consumed by expectant mothers in sufficient amounts early in pregnancy. The current WHO guidelines suggest that iodized salt, provided that it is universally available (i.e. 90% of households have access to iodized salt), will provide sufficient iodine for women during pregnancy [29]. Urinary iodine concentrations in school children are recommended as an indicator for iodine status of the total population. However, as we have previously shown in a study comparing UI in pairs of pregnant women and their school-aged children in Thailand, there is reason to believe that children receive sufficient iodine with salt iodization, whereas their mothers do not [30]. In that case, targeted supplementation of pregnant women would be a good additional strategy, even in areas where iodized salt has already been implemented. Additional studies in this and other settings are required to investigate this further.

Iodine supplementation studies in mildly deficient pregnant subjects mostly stopped before or at the moment of delivery [31]. These studies, all conducted in mildly deficient areas in Europe, have shown that iodine supplementation increases maternal urinary iodine (UI) excretion and reduces thyroid volume, as well as prevents increases in infant thyroid volume and thyroglobulin. In general, these studies suggest that maternal thyroid metabolism can cope with mild iodine deficiency [32]. Effects of maternal iodine supplementation on infant growth and development, however, have not yet been adequately addressed.

Three non-randomized studies conducted in Spain, a country with historic mild iodine deficiency, have been published in which children from supplemented and non-supplemented women were followed and tested over time. In one of these studies, children 18 months old born to women with low 24-hour levels, who were supplemented either from early gestation (4–6 weeks, n = 13), later gestation (12–14 weeks, n = 12) or after delivery (n = 19), were tested for their developmental quotient using the Brunet–Lézine scale. There was a significant trend in developmental quotient over the three groups, with the group longest exposed to iodine supplementation having the highest developmental quotient (101 vs. 92 vs. 87, P < 0.05) [33]. In another study, children from a group of pregnant women who had received iodine supplements from the first trimester of pregnancy onwards (n = 133) were compared with children from mothers who had not received iodine supplements (n = 61). Children were assessed by the Bayley Scales of Infant Development at the age of 2 years. Children from supplemented mothers had a 6.1 point higher Psychomotor Development Index score (P < 0.02), but the Mental Development Index score did not differ between the two groups [34]. In a third study, total iodine intake, both from diet and supplements, was assessed in a group of pregnant women and related to the PDI and MDI of their infants at one year of age. In contrast to the two other studies, it was found that children from mothers with high intake of iodine from supplements (>150 μg/d) had a 5.2 lower PDI score [35]. Apart from the inconsistencies in outcomes between these studies, neither is equipped to provide hard evidence for any beneficial or harmful effects of maternal iodine supplementation on the mental and motor development of their offspring.

It is therefore still a question mark whether iodine supplementation during pregnancy should be recommended in areas of mild-to-moderate iodine deficiency. In order to investigate this, we have set up randomized controlled trials at two study sites (Bangkok, Thailand; and Bangalore, India) with the objective to determine the effects of daily oral iodine supplementation or placebo in pregnant women with mild-to-moderate ID on maternal and infant thyroid function, birth outcome and child development (the MITCH studies). Recruitment began in 2008. Pregnant women, <14 weeks of gestation, aged 18–40 years with singleton pregnancies and not receiving iodine supplements have been included in the study. Women with overt hypothyroidism (TSH > 6 mIU/L) have been excluded. Eligible women have been randomly assigned to receiving daily iodine supplements (200 μg) or identical placebo tablets until delivery. Pregnant women are followed up twice during pregnancy and at delivery. In total, 514 women have been included in Thailand, and 325 in India. Data collected from mothers include urinary iodine and thyroid hormone concentrations, as well as thyroid volume. Cord blood and heel stick blood (<72 h) is collected from the neonates for assessment of thyroid function. Other data collected from the infants include birth weight and height, Apgar scores, urinary iodine, and thyroid volume. The Neonatal Behavioral Assessment Scale (NBAS) is performed around 6 weeks of age, and the MDI and PDI are assessed with the Bayley Scales of Infant Development at 12 and 24 months of age. The last data are expected to be collected in November 2013.

In conclusion, up till now it is unknown whether maternal iodine supplementation in areas of mild-to-moderate iodine deficiency should be recommended. Outcomes of the ongoing trials are awaited to prove or disprove the safety and efficacy of iodine supplementation in pregnancy.

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